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CLINICAL practice, lipid emulsion is used commonly as a component of parenteral nutrition. Lipid emulsion also is used as therapy for severe cardiotoxicity secondary to accidental overdose of local anesthetics, an effect that has been confirmed in animals and humans. Because patients with local anesthetic-induced cardiac arrest are considered to be less responsive for standard resuscitation methods, this finding is striking, and currently infusion of lipid emulsion is considered the primary treatment for local anesthetic toxicity. In this issue of Anesthesiology, Rahman et al. report a new and potentially clinically relevant benefit of lipid emulsion therapy.

Classic preconditioning produces in the heart a state profoundly protected from ischemia-reperfusion injury; however, the prerequisite for knowing when the ischemic injury will occur has limited the clinical translation and relevance of preconditioning. Recently, a potentially more clinically relevant form of cardiac protection, termed postconditioning, has been described. Postconditioning involves the application of protective interventions (e.g., brief ischemia-reperfusion, volatile anesthetics, opioids, and other classic cardioprotective agents) after ischemia but before reperfusion.

Rahman et al. extend the list of postconditioning agents to include Intralipid (Sigma, St. Louis, MO). They show that lipid emulsion infusion just before reperfusion (i.e., postconditioning) protects from myocardial ischemia-reperfusion injury. Subsequent mechanistic studies define a role for glycogen synthase kinase-3β and the mitochondrial permeability transition pore (mPTP) in this response. Mitochondria, a source of cellular adenosine triphosphate, are increasingly implicated in cell survival and death signaling in the heart. In particular, the mPTP has been suggested as the final effector in cardiac myocyte protection. The mPTP opening in response to stress leads to an increase in mitochondrial membrane permeability to small molecules, resulting in cellular apoptosis and necrosis. Thus, regulating the mPTP opening has been considered to be a promising target for cardiac protection, and others have suggested the involvement of mPTP in postconditioning.

Postconditioning is mediated via a complex molecular signaling cascade involving the reperfusion injury salvage kinase and the survivor activating factor enhancement pathways. Rahman et al. implicate common survival pathways, such as PI3K-Akt and ERK, in lipid emulsion-induced protection. In addition, they link these upstream survival kinases to downstream regulation of glycogen synthase kinase-3β. Recent work has shown that increased phosphorylation of glycogen synthase kinase-3β reduces the affinity of the adenine nucleotide translocase for cyclophilin D, suggesting that assembly of the complex is targeted by protective signals to limit mPTP opening. Thus, there appears to be a direct link between survival kinase regulation and mPTP end effector function.

These intriguing findings by Rahman et al. leave us with some important questions to be addressed in future investigation. First, how does lipid emulsion activate survival kinases—via a direct effect or secondary to receptor stimulation? General protective interventions appear to signal through G-protein-coupled receptor pathways, including preconditioning and postconditioning via opioids, volatile anesthetics, and other cardioprotective agents. It would be important to determine whether lipid emulsion is sensitive to

Illustration: J. P. Rathmell/A. Johnson.
G-protein–coupled receptor inhibition. Second, does intralipid modulate membrane lipid composition to modulate cardiac protection? Signaling components involved in cardioprotection are localized in membrane microdomains (i.e., lipid rafts and caveolae) that are enriched in cholesterol and sphingolipids.16,17 A recent publication suggests there may be some link between lipid emulsion and caveolin18; however, a direct effect of lipid emulsion on caveolins was not tested in this study. Other studies show that perturbing caveolae can alter survival kinase signaling critical to protection from cardiac and neuronal ischemia–reperfusion injury.19–24 It would be interesting to know whether Intralipid, being a lipid emulsion, affects membrane microdomains such as lipid rafts and caveolae to produce protection. Third, does the protective effect of lipid emulsion identified in this study play some role in the effects of propofol (where 10% lipid emulsion is the vehicle) that have been noted in ischemia–reperfusion injury? The potential protective effects of propofol are controversial,25,26 and the lipid emulsion effects need to be considered separately from the potential direct effects of propofol. Studies using fospropofol (a water-soluble formulation of a phosphate ester prodrug of propofol) may be useful in resolving this issue.

In summary, the current study by Rahman et al. focuses on a potentially important role for lipid emulsion in cardiac protection. Additional studies are needed to focus on mechanisms and potential clinical trials in humans. If similar protective effects are demonstrated in patients, lipid emulsion may play a novel and important role as a therapeutic intervention for patients with ischemic heart disease.

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References


ANESTHESIOLOGY REFLECTIONS

Siker’s Mapleson-modified Boyle Apparatus for Halothane

After designing his namesake mirror laryngoscope, E. S. “Rick” Siker, M.D. (b. 1926), studied in Wales from 1955–1956 with Professor W. W. Mushin. Before departing Cardiff for Pittsburgh in October of 1956, Dr. Siker (left) “was presented with a Boyle’s anesthetic machine with a trichloroethylene vaporizer calibrated by Bill Mapleson to deliver precise concentrations of halothane.” Using that apparatus (right), Dr. Siker conducted America’s second large-scale clinical trial of halothane for general anesthesia. The 1973 American Society of Anesthesiologists (ASA) president and the recipient of ASA’s 1983 Distinguished Service Award, Dr. Siker has also served as the Anesthesia Patient Safety Foundation’s first executive director. He generously donated this historic Boyle Apparatus to the Wood Library-Museum of Anesthesiology. (Copyright © the American Society of Anesthesiologists, Inc. This image also appears in the Anesthesiology Reflections online collection available at www.anesthesiology.org.)

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